Cysts and Cancer

Introduction

This lesson combines the cystic diseases of adulthood with renal cell carcinoma because often, clinically, the choice will be to decide whether the thing on imaging is a cancer and warrants excisional biopsy, or whether the thing on imaging is just a cyst, and can be left alone. We're not going into the decision-making in the basic sciences. But in order to be comfortable making the decision clinically, you should be aware of some of the cysts and some of the cancers that are seen. Wilms' tumor, aka nephroblastoma, is covered in this lesson because it is not a congenital defect, though it does occur in children. You are more likely to be tested on Wilms' tumor against congenital defects, though we are teaching it to you here under cancer.

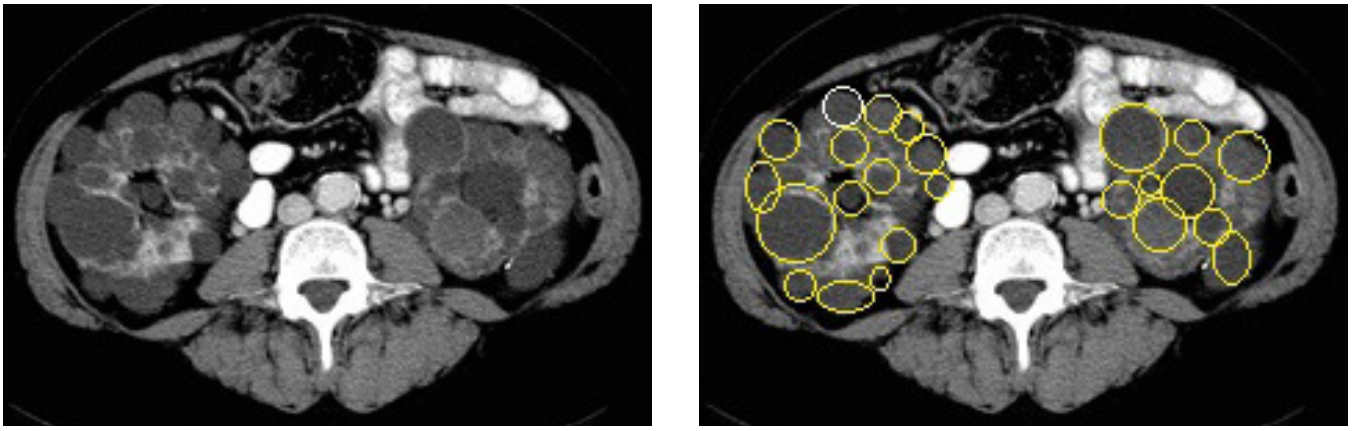
Autosomal Dominant Polycystic Kidney Disease

This is a devastating and yet common genetic disease. Because it is **autosomal dominant**, it takes only one copy of the mutated allele to produce the disease, and because the cysts do not become apparent until adulthood, the affected person has time to procreate, potentially passing the disorder on to the next generation before symptoms become evident. This disorder affects **1 in 1,000** people. It is the **leading cause of dialysis** in the United States. The gene mutation is often **PKD1** (notice no "h" as there was in the recessive type) on **chromosome 16**, which codes for a protein called **polycystin 1**. Other mutations found in PKD2, polycystin 2, have been implicated. Patients are born with cysts. They are too small to see with ultrasound. They do not cause any defect in the development of baby in utero, so there is no oligohydramnios. In an infant, because the cysts are so small, they do not impair renal function, so labs are normal.

Cysts begin to grow in adulthood. At first, they are few, small, and asymptomatic. The cysts **replace normal parenchyma**. As renal function begins to get impaired, the patient develops **hypertension**, which will be progressive and difficult to control, just as in any patient approaching end-stage renal disease (ESRD). As more cysts appear, and as they begin to enlarge, the cysts are predisposed to **infection** (pyelonephritis) because the urine in the cysts is stagnant, **stones** (flank pain), and **hemorrhage** (hematuria). The late-stage presentation is, classically, **chronic renal failure, hypertension**, and **enlarged kidneys**. Most ESRD kidneys are small. The large-sized kidneys and ESRD are classic for this disease. End-stage renal disease does not occur until the 40s or 50s. An **ultrasound** or **CT** will demonstrate **enlarged kidneys** replaced by many **cysts**.

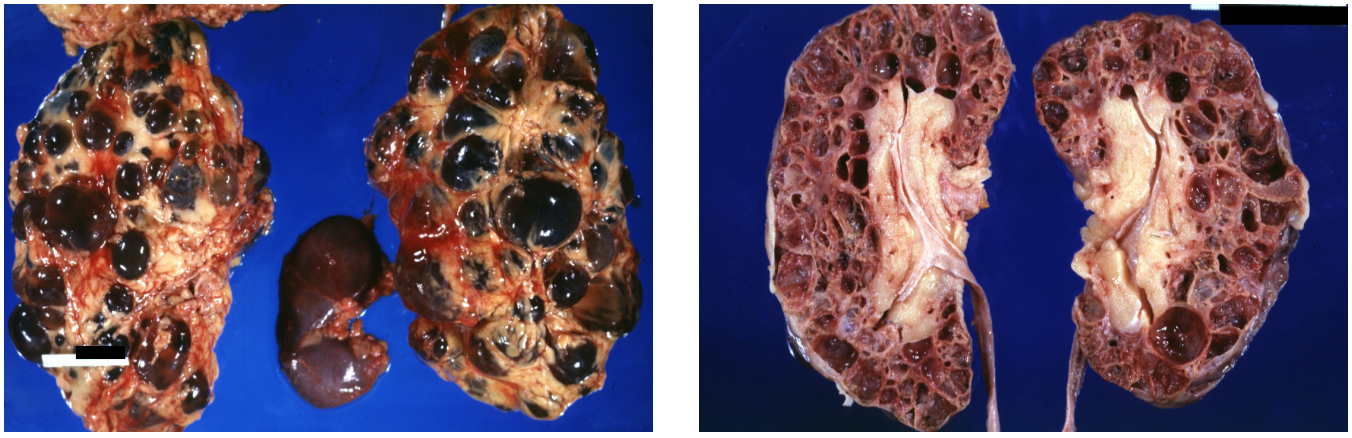
On gross pathology the kidneys will be **massively enlarged**, with **circular cysts** everywhere—medulla and cortex. Little parenchyma will remain. The large bulging cysts could be filled with urine (yellow), pus (white), or blood (red). On histology, the cysts arise from **tubular epithelial cells**, and there will be **circular cysts** with **normal nephrons between**.

Extrarenal manifestations include **liver cysts**, **pancreatic cysts**, and **berry aneurysms** in the circle of Willis.



(a) (b)

Figure 7.1: Radiology of ADPKD
(a) CT demonstrating numerous cysts and enlarged kidneys. (b) The same thing again with the cysts pointed out.



(a) (b)

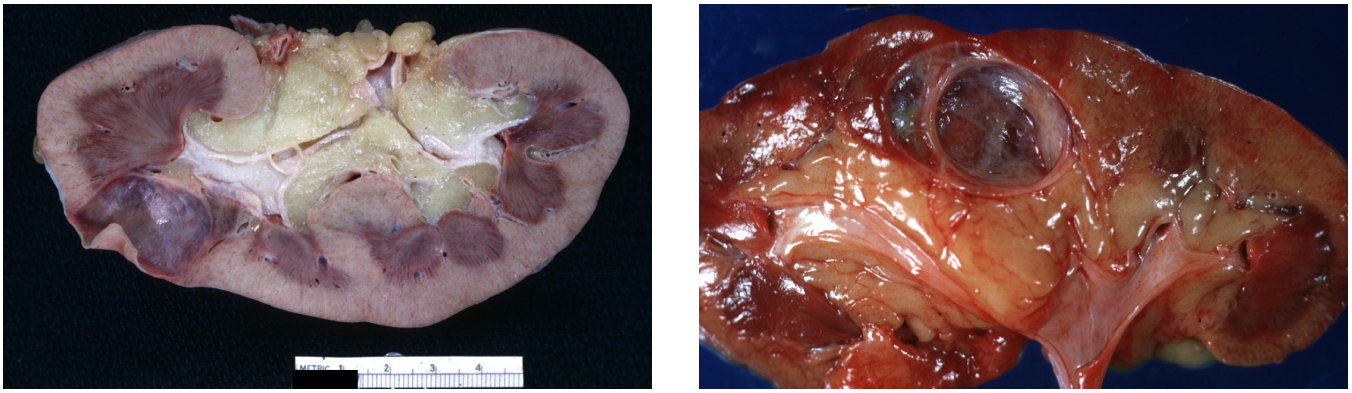
Figure 7.2: ADPKD
(a) Autosomal dominant polycystic kidney disease with a normal kidney to demonstrate how large they can get. (b) Cut kidney revealing the internal aspects of the cysts.

Acquired Polycystic Disease

Adults with mutation in the PKD1 or PKD2 gene end up with cysts, and then go on dialysis. Adults who are on dialysis can get cysts after going on dialysis, caused by dialysis. So if you see someone while on dialysis, and get imaging of their abdomen, you might find yourself with some renal cysts. Acquired (dialysis-associated) cystic disease is diseased kidneys that **develop cysts because of prolonged dialysis**, whereas ADPKD is kidneys that **develop cysts that necessitate dialysis**. Both have cysts that occur in the **cortex and medulla**. Both can contain urine, pus, or blood. Both can present with hematuria, flank pain, or pyelo. Both will have enlarged kidneys with circular cysts. But it is the **order of events** that produced the cysts, and possibly the severity (the longer on dialysis, the larger and more acquired cysts can form) that separate them. Because the acquired cysts of dialysis are in effect dysplastic tissue, they can progress to **renal cell carcinoma**.

Simple Cysts

Kidneys can get cysts. These cysts are not associated with disease, do not progress to cancer, and may cause no symptoms. Because they are cysts, they could bleed or get infected, but usually they don't. Simple cysts are **small** and **always cortical**. They are often an **incidental finding on abdominal imaging**. Because they are **few** and **small**, they require no follow-up, no workup, and can be ignored. This is especially true with an **older patient** who has no kidney disease and is without symptoms. They are **translucent**, clear, and **lined by a single membrane**. This is compared to complex cysts which are large, multi-echogenic (different colors on imaging) or loculated. Complex cysts are difficult to differentiate from cancer. Simple cysts are ignored.



(a) (b)

Figure 7.3: Cystic Disease
(a) Very good example of single cortical cyst ischemic kidney (lower left). (b) Large serous cyst replacing the renal pyramid but leaving the cortex intact.

Medullary 1: Innocuous Medullary-Sponge Kidney

This occurs in **adults** and has an **unknown pathogenesis**. There are **medullary cysts** found incidentally on imaging. A simple cyst was an incidental cortical cyst. Medullary-sponge kidney is the medullary version of simple cysts. The cysts are lined by **cuboid epithelium**, the same thing as the renal tubules. They aren't malignant, but can be mistaken for malignancy because simple cysts, the ones you don't have to worry about, are always cortical.

Medullary 2: Malicious Medullary Cystic Disease or Nephronophthisis-Medullary Disease

The name is hard to say. Not much is known about it. But watch out for similarities. This disease is best discussed as a review, in context of the other diseases we've studied, acting as a comparison disease.

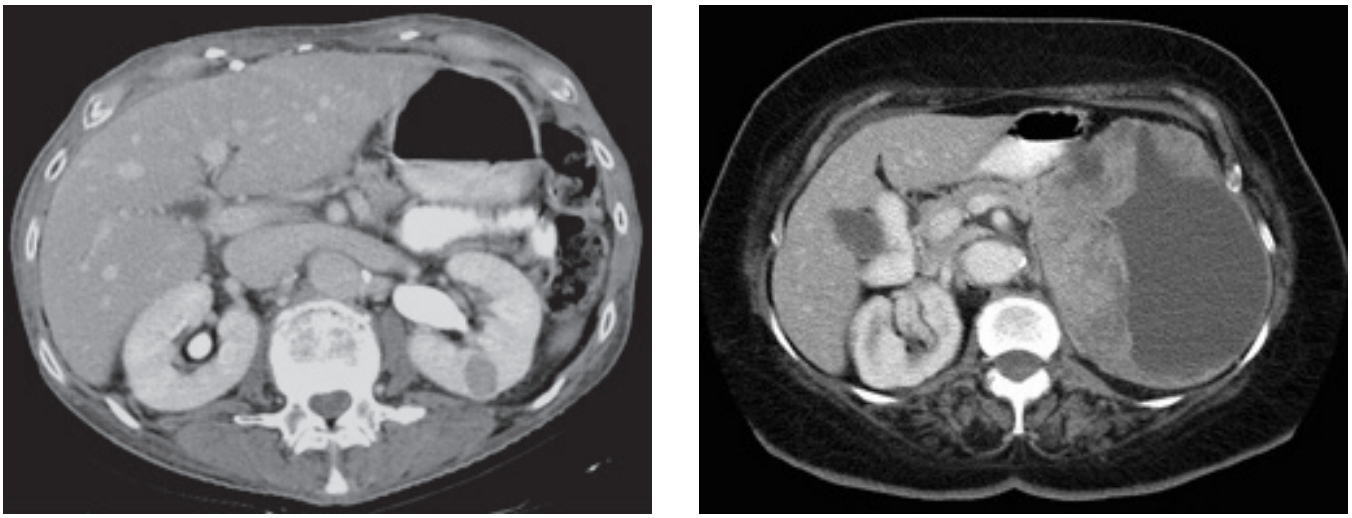
ARPKD and cystic dysplasia cause end-stage renal disease in children (months). The cysts are radial, and are everywhere.

ADPKD and acquired cystic disease are seen in adults (50s), and both require dialysis. The cysts are circular and are anywhere.

Medullary cystic disease causes end-stage renal disease in young adults (20s). The cysts are **cortico-medullary** and are **circular**. Medullary cystic diseases are characterized by **cuboidal epithelium** lining. Medullary-sponge kidney has **no fibrosis**, while malicious-medullary has **surrounding inflammation and fibrosis**.

Cancer

The two tumors you need to know about are the **Wilms' tumor** in **children** and **renal cell carcinoma** in **adults**. After these two tumors, there are some benign findings we'll cover. The important thing is that even though there are only two malignancies of importance, and you can know which it is just by the age of the patient, because there are so many details about each one, they become excellent fodder for hinge questions on licensure examinations. The challenge won't be identifying which malignancy it is, but rather all the directions a test question can take you. There are so many associations, it is tough to keep them all straight.



(a) (b)

Figure 7.4: Imaging of Cysts
(a) Simple cyst (the dark circle against the white kidney) on the left kidney (right side of image). (b) Large complex cystic mass in the upper pole of the left kidney. In the plane is a normal right kidney.

Renal Cell Carcinoma

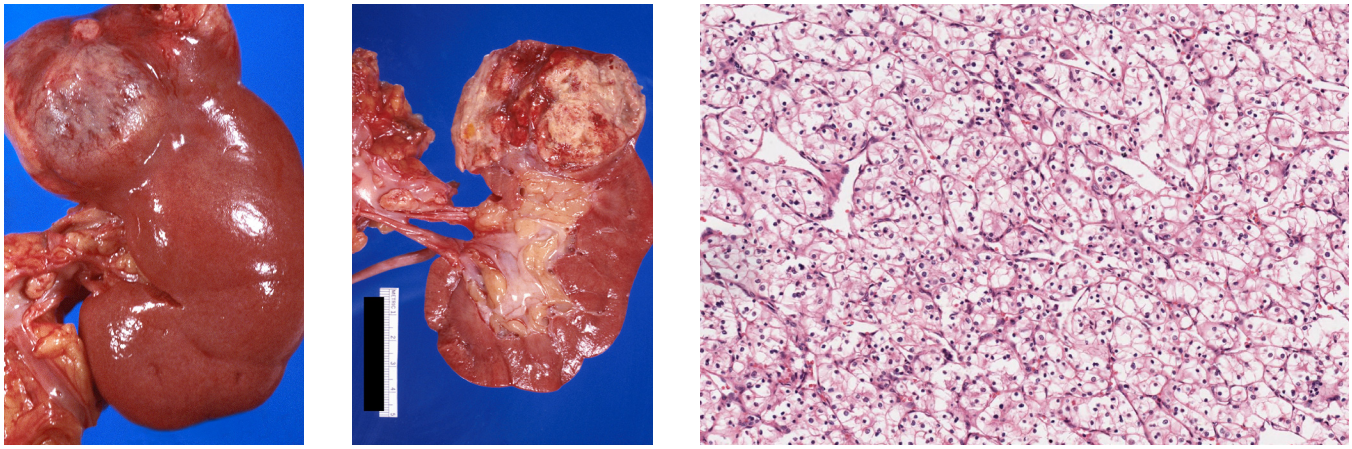
There are two pathways to getting renal cell carcinoma. Both involve some **loss of the VHL gene** on chromosome 3. The sporadic form of renal cell carcinoma is seen in **adults who smoke cigarettes**. The sporadic form is usually unilateral and of the superior pole of the kidney. The inherited form is called **Von Hippel–Lindau disease**, an **autosomal dominant** inherited mutation that leads to **inactivation** of the **VHL gene** via **hypermethylation**. In the inherited form, tumors occur in young patients, are numerous, and are often bilateral.

What is still taught is the **classic triad** (present in only about 10% of cases, so not classic, but "classic") of **flank pain, flank mass, and hematuria**.

Instead, what usually happens is either a **metastatic lesion** is found (poor prognosis), **abdominal imaging** for something else discovers a lesion, or there will be some **paraneoplastic syndrome**.

The tumor **spreads hematogenously**. It invades into the kidney and grows out from the capsule, replacing parenchyma with tumor. But it metastasizes not by going through the lymph nodes, but by hematogenous invasion into the **renal vein**. Stage 3 cancer is **in the renal vein**; stage 4 is **distant from the kidney**. And this is how the exam will test your knowledge of renal vascular anatomy. Because the adrenal vein, gonadal vein, and the renal vein come together before draining into the IVC on the left, a left-sided malignancy can result in obstruction of venous outflow from the gonadal vein (varicocele) or adrenal vein (adrenal vein thrombosis and infarction of the adrenal gland).

Paraneoplastic syndromes are **endocrine consequences** when a tumor has the ability to **produce hormones without regulation**. The kidney produces **erythropoietin**, which, if produced in excess, would lead to **polycythemia** (excess red blood cells). The kidney produces **renin**, which, if produced in excess, would cause **hypertension**. Renal cell carcinoma can also produce **ACTH**, which would lead to upregulation of cortisol, leading to **Cushing's syndrome** (not "disease" meaning of-the-pituitary, but "syndrome" meaning clinical features). Hypercalcemia and androgenization can also occur.



(a) (b) (c)

Figure 7.5: Renal Cell Carcinoma
Renal Cell Carcinoma (a) Gross (b) Histo (c) Path.

On gross anatomy, there will be a **single mass** (unless VHL) in the **upper pole** of the kidney. The tumors will be **yellow in color** with hemorrhage and necrosis, but especially with yellow **invasion into the kidney** and renal vein. On micro, there are three subtypes.

Clear-cell renal cell carcinoma is the most common and is the only renal cell carcinoma subtype we're going to teach you. It is called clear-cell because the cells have a darkly staining nucleus surrounded by **large amounts of clear cytoplasm** that actually have the appearance of foam-like fat cells. These fat cells give the renal cell carcinoma its yellow appearance. The cells derive from the proximal tubular epithelium. This is refractory to chemotherapy and radiation. Treatment is with nephrectomy. Chemo and radiation can be attempted. Because of the late stage at diagnosis, prognosis is usually abysmal for renal cell.

Wilms' Tumor (Nephroblastoma), Kidney Cancer of Children

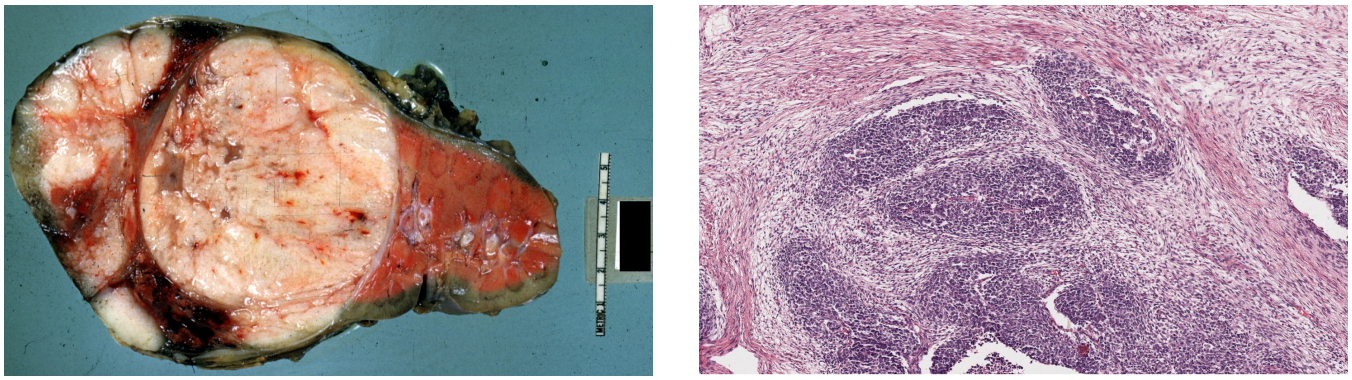
This tumor occurs in children, with a peak between **2 and 5 years of age**. There is a genetic association with the Wilms' tumor gene, **WT1** and **WT2**. The nephroblastoma can get quite large. In children, you can rely on the abdominal exam, and the child will present with **massive abdominal mass** and a characteristic syndrome. Because these tumors are capable of producing renin, young patients will have very high blood pressures for their age. There are named syndromes that result as a product of mutations of these genes.

WAGR syndrome is caused by a **deletion in WT1**. WAGR stands for Wilms' tumor, Aniridia (no iris), Genital abnormalities (ambiguous genitalia or cryptorchidism), and mental Retardation.

Denys-Drash syndrome (DDS) is associated with genital abnormalities and Wilms' tumor. It is a not-as-bad WAGR syndrome because it is a not-as-bad gene mutation. Instead of a deletion, there is only a mutation in the codon altering the protein. Still **WT1**.

Beckwith-Wiedemann syndrome (BWS) is caused by **imprinting** genetic disease involving **WT2**. It is an overgrowth disorder, which can result in macrosomia (big baby) and **hemihypertrophy** (one limb is bigger than the other). When there is an increased growth, growth factors are upregulated, tumor suppressors are downregulated, and uncontrolled growth increases the risk of cancer. The **hypertrophied kidney** is the one at risk for tumor.

On **gross**, you will see a **very large**, easily **demarcated** mass, **tan** in appearance, and always **unilateral**. On **micro**, you will see a **triphasic appearance—**three different histologic patterns will be visible simultaneously. The first is the **epithelial structures** that look like immature glomeruli and immature tubules—the kidney trying to build kidney, but it can't. The second is **blastema** (that was the word for the metanephros mass-that-will-become-kidney)—dark, blue, round cells of undifferentiated **embryonic tissue** with **mesenchymal spindle cells**. The third phase is the **stroma** consisting of clear elongated cells. **Ninety percent** of patients will achieve remission with **surgery** (nephrectomy).



(a) (b)

Figure 7.6: Wilms' Tumor (Nephroblastoma)
(a) Gross. (b) Histo.

Urothelial Carcinoma

The urothelial lining of the ureters and bladder is transitional cell. Bladder cancer is most commonly transitional cell carcinoma but can be squamous cell carcinoma. The ureters can have either as well. We are reserving the discussion of bladder cancer for the Bladder and Prostate series. We want you learning "renal cell carcinoma adults, Wilms' tumor kids" for kidney cancers.

Benign Tumors of the Kidney

Renal papillary adenomas are very common. They are small (**< 3 cm**), round, yellow nodules that must always be in the **cortex**. They arise from **tubular** or **papillary structures**. These are not simple cysts, though they are small and arise from tubule cells. They share the same chromosomal changes as renal cell carcinoma. They are single yellow structures in the cortex. It is actually quite difficult to assess, without a biopsy, whether the thing you are seeing is an early renal cell carcinoma or a benign papillary adenoma. In fact, it is possible that renal papillary adenomas represent a premalignant stage of renal cell carcinoma progression. Up to 25% of autopsies discover renal papillary adenoma. **Biopsy** without nephrectomy would be appropriate here, small enough so that there is a low suspicion for renal cell carcinoma.

Oncocytomas ("cortical adenomas") are large but benign tumors. When you see a **unilateral** mass on the kidney, and it is small, think renal papillary adenoma. When you see a unilateral mass on the kidney and it is huge, think renal cell carcinoma. But when that large unilateral mass that was

"obviously renal cell carcinoma" ends up being benign, being not renal cell carcinoma, chances are it is an oncocytoma. Oncocytomas have eosinophilic (**pink**) rather than clear cytoplasm, and appear **brown** on gross, not yellow.

Angiomyolipoma is the name given to a **renal hamartoma** that is associated with **tuberous sclerosis**. It is a tiny (< 2 cm), nonmalignant, grey-white **firm nodule** found within the **pyramids**. The tubers of the brain cause seizures, and are grey-white firm nodules in the brain. The same tubers can be in the kidney. (They aren't actually the same thing histologically; it just helps me to keep them straight this way.)

DISEASE	CHARACTER
Autosomal dominant polycystic kidney disease	*Patient*: **Adult** who is normal in youth, then **develops progressive HTN** and **progressive kidney** disease. End-stage is **flank mass**, hematuria or pyelo, and **ESRD** (50s). 1 in 1,000 patients *Path:* Autosomal **dominant**; mutation of **PKD1** (chr16, polycystin) and can be **PKD2** *Gross*: Massively enlarged kidneys, **bilateral**, **circular nonuniform cysts** everywhere *Histo*: Large circular cysts with **normal glomeruli in between** *Downstream:* Most common cause of dialysis. **Extrarenal cysts** are present in liver and pancreas. Cysts of the cerebral arteries = fatal **berry aneurysms** (subarachnoid bleed)
Acquired cysts (dialysis-associated)	*Patient*: An **adult** who is **already on dialysis** who then develops a few cysts *Path*: Dialysis-induced dysplasia *Gross*: **Few**, large **circular cysts**, that can be medullary or cortical *Histo*: Few large cysts *Downstream*: Dysplasia can transform into **renal cell carcinoma**
Simple cysts	*Patient:* **Incidental** cortical cysts, generally found in elderly *Path*: Normal variant *Gross*: Small circular cysts in cortex *Histo*: Single-layered membrane *Downstream*: Benign
Medullary cystic (sponge)	*Patient:* **Incidental** medullary cysts *Path:* Unknown *Gross*: Small circular cysts at **cortico-medullary junction** *Histo*: **Cuboid epithelial**-lined cysts, **no fibrosis** *Downstream*: Typically a **benign outcome** with an **idiopathic cause**
Nephronophtithisis medullary	*Patient:* **Young adult** (20s) that develops **ESRD** *Path:* Juvenile form **NPH** (**nephrocystin**); both AD and AR inheritance patterns *Gross*: Large cysts at the **cortico-medullary junction** *Histo:* **Cuboid epithelial**-lined cysts, with surrounding **inflammation and fibrosis** *Downstream*: Progression to renal failure (ESRD); kidneys are small
Common risk shared by cysts	All cysts can **bleed** (hematuria), can get **infected** (pyelo), or develop **stones** (pain)

Table 7.1: Cystic Diseases Summary

DISEASE	CHARACTER
Angiomyolipoma	Hamartomas within in the kidney that are caused by **tuberous sclerosis** **Tiny** (< 2 cm) found in the **pyramids**
Renal papillary adenoma	Benign tiny tumor that doesn't really do anything **Small** (< 0.5 cm) found in the **cortex only**
Oncocytoma	Large benign tumor of the kidneys **Resection** is performed because we think it's renal cell When cut open, it is brown and cells have robust pink cytoplasm
Renal cell carcinoma	Kidney cancer **of adults**. ↑ risk with **smoking** (VHL gene mutation) or **Von Hippel–Lindau** (VHL gene hypermethylation) *Gross:* **Unilateral**, singular **large yellow** tumors of the cortex (VHL are bilateral) that **invade** *Micro:* Most commonly a **clear-cell carcinoma** (looks like a large fat cell) *Metastatic:* **Hematogenous spread** into the **renal vein** *Classic triad:* 10% of cases have **hematuria, flank pain, mass** *Paraneoplastic:* Polycythemia (EPO), HTN (renin), Cushing's (ACTH)
Wilms' tumor	A tumor of the kidneys in **children** with peak age of 2–5 years **Deletion** of **WT1** (chr11) is **WAGR** syndrome—Wilms', Aniridia, Genitals, Retardation **Mutation** of **WT1** is **DDS**—Wilms', Genitals **Mutation** of **WT2** is **BWS**—hemihypertrophy, enlarged kidney gets cancer **Huge mass** on a tiny kidney that is **easily palpable** abdominally 3 components = **Immature epithelium**, blastema (dark blue cells), and stromal component Excellent prognosis with the intervention of surgery, radiation, and chemo

Table 7.2: Kidney Cancers